Screening for Hepatocellular Carcinoma
Review and Perspective

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In patients with hepatocellular carcinoma, early diagnosis offers the only hope for resection and cure. Data from Asia, where it is closely associated with viral hepatitis, indicate that serum α-fetoprotein assay and abdominal ultrasonography are the most effective and feasible screening tests. These data may not be applicable in America, where most patients at risk for hepatocellular carcinoma have underlying alcoholic cirrhosis. Also, it is unclear whether resecting "curable" lesions prolongs survival, particularly in patients with cirrhosis. Screening trials are indicated to answer these questions. Preventing risk factors, however, especially hepatitis B viral disease, is of paramount importance throughout the world.

(Ellis JC: Screening for hepatocellular carcinoma—Review and perspective. West J Med 1988 Aug; 149:183-187)

Hepatocellular carcinoma (hepatoma) accounts for 90% of all primary liver carcinomas.[1] It is one of the most common malignant disorders in Japan,[2,3] Taiwan,[4] and other areas of Asia and Africa.[5-8] Hepatocellular carcinoma is heterogeneous in its pathogenesis, clinical presentation, virulence, and prognosis. In the United States and Western Europe, greater than 90% of hepatomas arise in the presence of alcoholic cirrhosis.[2,4,9-11] In the "hepatic-cancer belt" of Asia and Africa and in the Pacific Islands, as many as 80% of patients with this malignant disorder are positive for the hepatitis B surface antigen (HBsAg) and as many as 40% do not have cirrhosis.[9] In areas endemic for hepatitis B, such as Taiwan, where the HBsAg carrier rate is as high as 15% to 20%, there is overwhelming evidence tying chronic carriage of HBsAg to hepatocellular carcinoma.[12-14] Perinatal transmission is responsible for as many as 40% of carriers. Moreover, up to 90% of infants born to mothers positive for the hepatitis B e antigen become carriers.[15] These patients have a greater than 200-fold risk of hepatoma developing in early adulthood and middle age.[16] With the recent influx of nearly 1 million Southeast Asian refugees, there will be a substantial increase in this country of those at risk for hepatocellular carcinoma.[17] This will add a new dimension to the pressing need for an organized approach to preventing and treating the disorder.

Resection offers the only hope for cure. Resectability is determined by the location and size of the tumor, symptoms, extent of local spread, and severity of underlying liver disease.[11] Screening programs predicated on the assumption that it is essential to find the tumor as early as possible have produced disparate results.[2,8,18-20] This may be due to the diverse nature of the carcinoma, the varying availability of medical care, the use of different screening regimens, and problems with patient compliance.

A full understanding of available screening modalities may guide decisions regarding their use in patients at risk for hepatocellular carcinoma.

Available Screening Tests

α-Fetoprotein Level

α-Fetoprotein is a serum protein found in high concentrations in fetal and maternal blood. Normal levels range from 0 to 5 ng per ml. Levels of 15 to 25 ng per ml and above are considered significantly elevated. Levels as high as, but rarely exceeding, 200 ng per ml may occur with chronic liver disease, hepatic regeneration, and tumors other than hepatocellular carcinoma. Concentrations of greater than 200 ng per ml increasingly suggest hepatoma. Specificity for the disorder is high at levels above 400 ng per ml.[21] The serum α-fetoprotein value is normal in 40% to 60% of patients with hepatocellular carcinoma in the US and Europe.[21,22] The correlation between the disorder and elevated α-fetoprotein levels is stronger in young male patients and in those with underlying hepatitis B viral disease. Serum concentrations generally parallel the size of the tumor and are often normal in "early" or "minute" (2 to 4 cm) hepatoma.[2]

Measurement of serum α-fetoprotein levels has been used for mass screening for hepatocellular carcinoma in Africa, Japan, and China. Okuda notes that screening programs in Africa failed to identify asymptomatic patients despite the strong association between hepatitis B-related hepatoma and α-fetoprotein levels.[8] This may be due to the undifferentiated, virulent nature of the disorder in this area. In China, where hepatocellular carcinoma tends to grow more slowly, Beasley and co-workers have documented the epidemiologic association between the hepatitis B virus and hepatoma.[16,23] Mass screening of 1.9 million people in Shanghai during 1971 to 1976 resulted in the identification of 300 patients with hepatocellular carcinoma, 134 of whom were asymptomatic.[24] Diagnosis resulted from a "positive" α-fetoprotein level—greater than 500 ng per ml in this study. Of these, 31 had resectable tumor, with a 57% three-year survival. Using α-fetoprotein assay in another mass screening of 1.2 million people in Qidong, Zhu identified

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ABBREVIATIONS USED IN TEXT
CT = computed tomographic
HBsAg = hepatitis B surface antigen

475 patients with hepatocellular carcinoma, 35% of whom were asymptomatic.[25]

Table 1 summarizes data from prospective studies. Heyward and colleagues screened 1,394 HBsAg-positive Alaskan Natives using serial α-fetoprotein assays.[18] Levels were greater than 25 ng per ml in 126. Nine had proven hepatocellular cancer. In all of these patients, α-fetoprotein levels were greater than 350 ng per ml. Six were asymptomatic and four had resectable tumor with curative intent. Liaw and associates screened 432 HBsAg-positive patients with α-fetoprotein assay and ultrasonography every three to six months, finding eight patients with asymptomatic hepatoma over a follow-up period of 6 to 85 months. Three cases were diagnosed by α-fetoprotein levels of greater than 400 ng per ml, while three were "suggested" by levels of 100 to 300 ng per ml. Two patients had "negative" levels—less than 20 ng per ml—and hepatoma was diagnosed by ultrasonogram.

Kobayashi and associates prospectively screened 95 persons with cirrhosis of mixed cause, doing α-fetoprotein assays every two months, an abdominal ultrasonogram every three months, and computed tomographic (CT) scan with angiography yearly.[2] Over a mean period of 4.2 years, eight cases of hepatocellular carcinoma were detected. Three patients had normal (less than 25 ng per ml) α-fetoprotein levels, two had "nondiagnostic" levels (less than 200 ng per ml), and only three had levels greater than 400 ng per ml. None of the tumors were resectable.

Obata and co-workers observed 115 patients with cirrhosis for as long as four years with serial α-fetoprotein assays every two months.[26] Ultrasonography, scintigraphy, and angiography were used as confirmatory tests when an α-fetoprotein level was elevated. Hepatocellular carcinoma developed in 27% of HBsAg-positive cirrhotic patients and in only 6% of seronegative patients with cirrhosis, underscoring the link between hepatitis B and hepatocellular carcinoma. The number of asymptomatic and resectable cases is not reported. Kubo and associates reported 31 cases of the disorder detected over a 1- to 14-year follow-up of at least 400 patients with chronic liver disease.[27] The α-fetoprotein level was a sensitive and specific marker, being greater than 400 ng per ml in 19 patients, more than 1,000 ng per ml in 16, and less than 400 ng per ml in only 6. But the majority were symptomatic at the time of diagnosis, and the smallest tumor detected by α-fetoprotein assay was 4 to 5 cm in diameter. The authors note that most patients were followed up sporadically, making any conclusion regarding the sensitivity of α-fetoprotein assay for detecting asymptomatic or treatable disease in these patients problematic.

The failure of α-fetoprotein assay to detect treatable disease in Japanese trials, along with other studies finding a poor correlation between α-fetoprotein levels and resectable hepatoma,[27-30] has led Japanese investigators to conclude that while α-fetoprotein levels may disclose asymptomatic hepatocellular carcinoma, the assay rarely detects treatable disease.[2,8,31,32] Larger prospective trials are warranted, however, especially in populations with a higher prevalence of alcoholic cirrhosis and chronic liver disease unrelated to hepatitis B. Mass screening in China and the work of Liaw and Heyward suggest that serial α-fetoprotein assays may detect asymptomatic and treatable disease in populations with a high incidence of underlying hepatitis B viral disease.

Ultrasonography

Several prospective studies from China and Japan indicate that ultrasonography may be more sensitive than α-fetoprotein assays for detecting resectable hepatocellular carcinoma, though the number of patients in these studies is small.[2,20] In a nonprospective evaluation of 230 asymptomatic patients with chronic liver disease, Okasaki and colleagues found 14 with hepatocellular carcinoma.[19] Seven of the tumors were smaller than 5 cm in diameter. Ultrasonography identified six of these, with a sensitivity and specificity of 86% and 99%, respectively. α-Fetoprotein values were greater than 400 ng per ml in only two of the patients with a lesion smaller than 5 cm. Maringhini and co-workers recently reported their study of 363 patients with cirrhosis and clinically suggestive hepatocellular carcinoma[33]; 146 proved to have the disorder. Ultrasonography showed a sensitivity and specificity of 90% and 93%, respectively. The sensitivity and specificity of an α-fetoprotein level of greater than 500 ng per ml were 49% and 100%, respectively. Of the 56 patients with carcinomatous lesions smaller than 5 cm, 91% were detected by ultrasonography and only 46% by α-fetoprotein assay, though resectability is not reported. Table 2 summarizes the above data.

Kobayashi and associates note that ultrasonographic accuracy is poor immediately below the diaphragm, especially in the superolateral aspect of the right hepatic lobe.[2] When a lesion is less than 2 cm and nonencapsulated, differentiating from hemangiomas, solitary regenerative nodules, or adenomas becomes problematic. In Japan, however, small carcinomas are frequently encapsulated and hypoechoic, making them more easily identifiable.[8,19] The Japanese have reported

TABLE 1.—*Screening for Hepatocellular Carcinoma (HCC)—Prospective Studies*

Source	Persons Screened, No.	Mean Screening Period, mo	HBsAg-Positive, %	Has Cirrhosis, %	HCC Identified, No.
Liaw et al, 1986[20]	432	27	100	<50	8
Heyward et al, 1985[18]	1,394	26	69	Unknown	9
Kobayashi et al, 1985[2]	95	50	35	100	8
Obata et al, 1980[26]	115	35	26	100	12

HBsAg=hepatitis B surface antigen

TABLE 2.—*α-Fetoprotein (AFP) Assay and Ultrasonography in the Diagnosis of 'Small'* or Resectable Hepatocellular Carcinoma (HCC)*

Source	HCC Identified, No.	'Small' HCC, No.	'Small' HCC Diagnosed by AFP Higher Than 400 ng/ml, No.	'Small' HCC Diagnosed by Ultrasound, No.
Liaw et al, 1986[20]	8	7	2	7
Kobayashi et al, 1985[2]	8	2	1	2
Heyward et al, 1985[18]	9	4	4	Not reported
Okasaki et al, 1984[19]—nonprospective	14	7	2	6
Maringhini et al, 1984[22]—nonprospective	146	56	26	51

*Less than 5 cm in diameter.

success in screening large numbers of middle-aged patients with chronic liver disease by using the "human dock" and employing the ultrasonograph as "one of the physical examinations like a stethoscope."[19]

Other Screening Modalities

Before the development of real-time ultrasonography, the only alternative to angiography was radiocolloid scintigraphy, which is relatively insensitive for hepatoma smaller than 3 cm.[8]

Sensitivity and specificity of CT scanning approximate that of ultrasonography because of the occasional presence of isodense tumors.[2,31] Angiocomputed tomography and infusion hepatic angiography provide more sensitivity, but invasiveness, expense, and radiation exposure limit their use to confirming possible neoplasms.[2]

Magnetic resonance imaging is useful in distinguishing hepatocellular carcinoma from small hemangiomas,[8,32] though its sensitivity in diagnosing the disorder is unknown and its expense considerable.

Laparoscopic sonography and biopsy have been used to diagnose hepatocellular carcinoma, though invasiveness prohibits their use as screening tests.

Des-γ-carboxy prothrombin accumulates in the absence of vitamin K or when vitamin K-dependent carboxylase activity is antagonized by the use of warfarin. Liebman and colleagues[34] and Soulier and co-workers[35] found significantly elevated des-γ-carboxy-prothrombin levels in 90% and 74%, respectively, of patients with known hepatocellular carcinoma. Des-γ-carboxy-prothrombin levels were most often normal or insignificantly elevated in cases of cirrhosis, chronic active hepatitis, and metastatic disease, suggesting a possible specificity for hepatocellular carcinoma. Still, it is unclear whether abnormal prothrombin is released because of derangements within the tumor or because of acquired carboxylase deficiency associated with severely impaired hepatic function.[36] As of yet, conclusions cannot be drawn regarding the sensitivity or specificity of des-γ-carboxy prothrombin in detecting treatable hepatocellular carcinoma.

Perspective—Will Early Identification Make a Difference?

The question of the resectability of hepatocellular carcinomas has been addressed by Ronald Malt:

> Since most hepatic-cell carcinomas in the Western Hemisphere arise as multicentric neoplasms in persons with alcoholic cirrhosis, no operation to remove them is reasonable, because of the extent of disease, the poor hepatic reserve, and the presence of portal hypertension.[11]

He adds, however,

> three categories of carcinoma must be considered for aggressive resection: carcinomas [resulting] from sex-hormone therapy . . .; localized carcinomas in patients with good hepatic function, especially those living in the "hepatic-cancer belt" of Africa and Asia; and some "minimal" hepatic carcinomas, even those in cirrhotic patients.

Lin and associates report that of 33 patients with cirrhosis who underwent resection of hepatocellular carcinoma, postoperative hepatic failure developed in 40% (13), and two thirds of those who underwent right lobectomy died of hepatic failure.[37] They attribute these results to poor hepatic reserve and the inability of the cirrhotic liver to undergo compensatory hypertrophy.

Nagasue and co-workers resected hepatomas in 118 patients, 101 of whom had cirrhosis[10]; 70% were Childs's class A. Most tumors were "minimal"—less than 3 cm in diameter—possibly showing the efficacy of Japan's screening programs. The two- and four-year survival rates of nearly 80% in patients without cirrhosis approximated the 88% three-year survival rate in the US series of Fortner and colleagues of 13 noncirrhotic patients who underwent curative resection for hepatocellular carcinoma.[38] Nagasue reported two- and four-year survival rates of 55% and 34%, respectively, in patients with cirrhosis.[10] The series of 109 patients of Lee and associates was divided into 47 symptomatic and 62 asymptomatic patients.[39] The latter group included 89% with cirrhosis and had a four-year survival of 44%. Only 8% of the symptomatic patients survived four years.[39] In Wu and co-workers' series of 180 patients, three- and five-year survival rates were 37% and 16%, respectively.[40]

TABLE 3.—*Operative Mortality and Long-term Survival in Selected Series of Resections of Primary Liver Cancer*

Source	Cases, No.	Cirrhosis Present, %	Survival at 2 Years, %	Survival at 4-5 Years, % (yr)	Operative Mortality, %
Lee et al, 1986[39]					
Symptomatic patients	47	32	52	8 (4)	0
Asymptomatic patients	62	89	80	44 (4)	3
Nagasue et al, 1986[10]	94	86	56	35 (4)	14
Wu et al, 1980[40]	181	70	37	16 (5)	9

Can these data be extrapolated to North American patients with hepatocellular carcinoma, most of whom have underlying alcoholic cirrhosis? Though alcoholic liver disease is still not the major cause of cirrhosis in Japan, it has been increasing dramatically; in one study, 52% of Japanese patients with hepatoma were heavy drinkers.[41,42] While cirrhosis was present in greater than 80% of both Lee's and Nagasue's groups, however, the overwhelming incidence of hepatitis B viral disease in the former and the predominant incidence of chronic viral hepatitis in the latter's population make extrapolating to North American patients problematic. Table 3 summarizes the operative mortality and long-term survival in selected series of patients undergoing resection for hepatocellular carcinoma.

An important concept addressed by Okuda is that a "small" hepatoma is not necessarily an "early" one.[8] Growth rates vary enormously, as described by Sheu and associates, who observed that a 1-cm lesion may take 9.8 months to 10.7 years to reach 10 cm in size.[43] Some hepatocellular carcinomas remain unchanged for many years, and survival for years without treatment is reported.[8]

Ebara and colleagues studied the natural history of minute hepatomas—less than 3 cm in diameter—finding occasional slow growth and a 90% one-year survival, 55% two-year survival, and 13% three-year survival.[44] Their 22 patients were felt to have underlying severe disease (most often cirrhosis) that precluded resection. It is interesting that Nagasue and co-workers also found a 55% two-year survival rate in their patients—most of whom were of a higher Childs's class—who underwent resection for cure.[10] While the latter's three- and four-year survival rates were superior and this comparison does not approximate a randomized, controlled trial, the survival data in patients with resected "minute" hepatomas, particularly in those with cirrhosis, should be interpreted cautiously.

Conclusion

Hepatocellular carcinoma is a diverse disease for which the only cure is resection. The presence of symptoms or a tumor size larger than 6 cm most often indicates unresectability. Serum α-fetoprotein assays and hepatic ultrasonography are effective in identifying asymptomatic, resectable neoplasms in certain populations predisposed to hepatic carcinoma by hepatitis B viral disease.[2,18,20,24,31] Recommended regimens are not well defined, though Kobayashi and associates recommend measuring serum α-fetoprotein levels every two months and doing an ultrasound examination every three months in high-risk Japanese patients.[2] Due, however, to the varying association between serum α-fetoprotein levels and liver disease of different causes and the heterogeneity of hepatomas, these data are not clearly applicable to the majority of American patients at risk for the disorder.

In a recent National Institutes of Health conference, Di Bisceglie and colleagues tentatively proposed measuring α-fetoproteins every three to four months and doing hepatic ultrasonography every four to six months in high-risk patients—including those with replicative hepatitis B infection, cirrhosis, or childhood hepatitis B infection—and doing ultrasonography annually in some lower risk patients.[45] As they noted, these guidelines are not proven but may be justifiable in patients with chronic hepatitis B viral disease. Most Americans at risk for hepatocellular carcinoma, however, have alcoholic cirrhosis. Their inclusion in such a program would incur enormous expense and is not justified, as it is unknown whether such screening will influence therapy or survival.

When small lesions of a suggestive but questionable nature are identified by any means, more frequent serial α-fetoprotein measurements and higher-resolution studies such as CT scanning may be used. Laparoscopic biopsy is indicated in selected cases. A serum des-γ-carboxy-prothrombin level may be a sensitive screening test for hepatocellular carcinoma. Its specificity and sensitivity in identifying asymptomatic, resectable disease are unknown. Four-year survival of greater than 80% has been documented in selected noncirrhotic patients undergoing resection for hepatoma. It is possible to resect hepatocellular carcinoma in patients with cirrhosis, though perioperative and postoperative mortality rates are much higher. Whether resection prolongs survival in patients with cirrhosis is unknown.

Preventing a predisposing factor has become feasible, however. We will see more patients from areas with a high prevalence of chronic hepatitis B viral disease. Physicians should be aware of guidelines regarding screening of patients for hepatitis B surface antigen,[46] especially pregnant women from areas endemic for hepatitis B,[47,48] and recommendations regarding vaccinating persons at risk for chronic infection, especially neonates with HBsAg-positive mothers.[49-52]

Ongoing and future trials may elucidate the role of screening for hepatocellular carcinoma in this country. Only awareness of the pathogenesis and risk factors, however, along with diligence in implementing preventive measures, will reduce the mortality from this disease.

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Book Review

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Dubois' Lupus Erythematosus

Edited by Daniel J. Wallace, MD, Assistant Clinical Professor of Medicine, University of California, Los Angeles; Attending Physician, Cedars-Sinai Medical Center, Los Angeles; and Chief Rheumatology Consultant, City of Hope, Duarte, California, and Edmund L. Dubois, MD (Deceased), Clinical Professor of Medicine, University of Southern California School of Medicine, and Director, Collagen Disease Clinic, Los Angeles County-USC Medical Center, Los Angeles. Lea & Febiger, 600 Washington Square, Philadelphia, PA 19106-4198, 1987. 749 pages, $98.50.

This third edition of Dubois' textbook stands as a tribute to the man who fathered this monumental undertaking and who was working on the third edition at the time of his death. Edmund Dubois devoted his professional career to the care of persons with lupus erythematosus in its many varieties and left a heritage of careful clinical observations to guide physicians at all levels of familiarity with this challenging group of illnesses.

Daniel J. Wallace, co-author of this third edition, and Francisco P. Quismorio, Jr, and James R. Klinenberg, Associate Editors, have, with Dr Dubois, produced a volume vastly improved over the revised second edition of 1976. With relatively few other experts, they have provided a thorough review of the historical, epidemiologic, and classification milestones that brought us to our present less than satisfactory overview of this complex family of illnesses. The current concept of an immunologic basis for lupus in humans and in mice is woven through the chapters on "Autoimmunity" and "Animal Models of Systemic Lupus Erythematosus." Although there is still a chapter on the lupus erythematosus cell test, a procedure widely unavailable in part because of its uneconomical resistance to automation, the more widely available serologic tests that frequently aid in diagnosis and management are thoroughly presented. The chapter on "Lupus Anticoagulant and Other Hemostatic Problems" by Rapaport and Feinstein elucidates an area of possible autoimmunity clearly not limited to systemic lupus erythematosus, but one that casts new light on old clinical observations.

Chapters five and seven in particular will be of interest to the widely varied audience of physicians who treat these patients. Sections provide the physician with material for the patient and directed to the problems of coping with a potentially fatal, chronic illness. The chapter on drug management, as well as the discussion of the use of renal biopsy, provide a comprehensive review but leave the readers, appropriately, to make up their own minds in a particular situation.

This third edition strikes this reviewer as a fitting tribute to the life's work of Edmund Dubois and will serve the clinician and clinical investigator with a plethora of suggestions for management and for future clinical investigations, which I am sure would have pleased the senior author.

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